

### **REMARKS**

Claims 19-41 and 43-46 were pending prior to this response. By the present communication, no claims are added or cancelled and claims 19, 24, and 41 have been amended to define Applicants' invention with greater particularity. The amendments add no new matter, the claim amendments being fully supported by the specification and original claims. Accordingly, claims 19-41, and 43-46 are currently pending.

#### **The Rejection under 35 U.S.C. § 112, Second Paragraph**

Applicants respectfully traverse the rejection of claim 24 as allegedly being indefinite under 35 U.S.C. § 112, second paragraph, for lack of antecedent basis for the phrase "the procaryotic cell." To overcome the rejection, Applicants have amended claim 24 to move dependency from claim 19 to claim 22, as recommended by the Examiner. In view of the amendment to claim 24, Applicants submit that the pending claims meet all requirements under 35 U.S.C. § 112, second paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

#### **The Rejection under 35 U.S.C. § 112, First Paragraph**

Applicants respectfully traverse the rejection of claims 19-41 and 43-46 as failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph, for allegedly introducing new matter. The rejection is based on the Examiner's assertion that no support can be found "in the claims, specification or drawings as originally filed" (Office Action, page 3) for the recitation in claim 41 of the phrase: "the bioactivity encoded by the DNA possesses the bioactivity of interest at a temperature at least 10 °C below the temperature of optimal activity of the bioactivity encoded by the wild-type DNA" and for the recitation in claim 19 of the phrase "naturally occurring." However, Applicants respectfully submit that the phrases at issue do not constitute new matter.

The original claims are deemed to constitute original disclosure in a patent application. Applicants submit that support for the phrase at issue in claim 41, which has been amended to

place dependency upon claim 40 is found in original claims 1 and 18 (now cancelled). Original claim 18 recites:

“The method of claim 1, including the additional steps of: subjecting an enzyme encoded by the DNA identified in step d) to directed evolution comprising the steps of:

- a) subjecting the enzyme to non-directed mutagenesis; and
- b) screening mutant enzymes produced in step a) for a mutant enzyme that is stable at a temperature of [sic] at least in the range of about 60°C and that has functioning enzymatic activity at a temperature at least 10°C below its optimal temperature range and that catalyzes a greater amount of a catalytic substrate per a defined unit of time than the enzyme of step a).”

Original claim 1(a), from which claim 18 originally depended requires that the DNA encoding the enzyme is obtained from “prokaryotic genomic DNA samples” and is subjected to “directed evolution” to lower the temperature of optimal activity by 10°C. Genomic DNA samples are by definition “wild type” and introduction of “at least one nucleotide mutation” as required by present claim 40, from which claim 41 depends is a type of directed evolution. Thus, Applicants submit that the combination of original claims 1 and 18 provide support for the phrase at issue in amended claim 41.

With regard to the Examiner’s assertion that no support can be found for the term “naturally occurring” as recited in claim 19, Applicants respectfully submit that support for this phrase is provided by the requirement of a starting material of “prokaryotic genomic DNA samples” in original claim 1. Genomic DNA samples are by definition “naturally occurring.” In addition, the Specification at page 7, line 14 provides support for the term “naturally occurring.” in the recitation: “Preferably ‘environmental libraries’ which represent the collective genomes of naturally occurring microorganisms are generated” (Specification, page 7, lines 12-14; see also page 17, 7 lines from the bottom, and page. 22, first paragraph of the Detailed Description.) Thus the combination of original claim 1 and the above noted passages from the Specification provide support for the phrase “naturally occurring” in claim 19.

In view of Applicants' showing of support in the specification and original claims for the terms at issue, reconsideration and withdrawal of the rejection under the written description requirement of 35 U.S.C. § 112, first paragraph, are respectfully requested.

**The Rejection under 35 U.S.C. § 102(b)**

Applicants respectfully traverse the rejection of claims 19, 20, 22, 24-29, 35, 37-39 and 43-45 under 35 U.S.C. § 102(b) as allegedly being anticipated by Thompson et al. (U.S. Patent 5,824,485; hereinafter "Thompson") as originally applied in the Office Action mailed herein December 07, 1999 and maintained in a subsequent Office Action mailed October 10, 2000. Applicants submit that the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, distinguish over Thompson at least by requiring that the bioactivity or biomolecule of interest be, not only naturally occurring, but also provided by the DNA of a single one of the organisms in the sample. Thus, Applicants' invention, as defined by amended claim 19, is not the purposeful creation of novel activities or pathways by combinatorial techniques, but rather expression cloning of naturally occurring DNA derived from a mixed population of organisms to produce libraries of naturally occurring activities or gene clusters or pathways or genes from a single organism as found in nature, without manipulation. The donor DNAs in Applicants' library have not been rearranged or recombined in a laboratory setting for the purpose of creating new, combinatorially produced, pathways.

Applicants disagree with the Examiner's position that the following passage from Thompson illustrates that Thompson's disclosure meets the requirements of Applicants' methods for identifying a "naturally occurring" bioactivity or biomolecule, as defined by amended claim 19, especially the requirement in claim 19 that "each clone contains DNA from a single one of the organisms." The passage from Thompson quoted by the Examiner as illustrating that Thompson screens "naturally occurring" DNA states:

. . . “[t]he naturally-occurring pathways of the donor organisms may thus be reconstituted in the host organism” such that “[t]he metabolic pathways of the donor organism may also interact with metabolic pathways resident in the host organism to generate novel compounds or compounds not normally produced by the host organism” (column 5, top).”

(Office Action, page 8). Applicants disagree that this passage from Thompson illustrates the term “naturally occurring” as used in Applicants specification and claims. In fact, Thompson here describes a species of “combinatorial library” wherein DNA native to the host combines with DNA obtained from the donor organism to produce a “novel compound”, such as a compound produced *in the combination* of metabolic pathways in the host and donor organism.

Applicants provide extrinsic evidence in support of the meaning of “combinatorial” as used in Thompson to distinguish such teaching from Applicants’ teaching and claims directed to screening of naturally occurring molecules. Exhibit A is a print out from an internet site that includes a description of Neugenesis’ combinatorial biology technology, which creates “combinatorial panels of heavy and light chains of a heteromeric protein and to build libraries of diverse, new, fully assembled proteins. Variants of each subunit gene are generated within the host by Neugenesis’ proprietary technology.” (<http://www.neugenesis.com/>) Clearly, Applicants’ claims are not directed to combinatorial approaches to identifying enzyme activities encoded by naturally occurring gene clusters, since Applicants are not manipulating the DNA to generate variants.

Exhibit B is a printout from the internet site of the Koide Group, from University of Pittsburgh (<http://www.pitt.edu/~sparano/group/>). As you will note, the study of Natural Products is separate and distinct from the study of Combinatorial Libraries. Exhibit C provides a glossary of terms used in Medicinal Chemistry. On page 4, the term combinatorial synthesis is described as “...combining sets of building blocks” e.g., ligating together individual genes of a gene cluster.

Thus, in view of Thompson's use of the combined metabolic pathways of host and donor organism to generate fluorescence indicative of the presence of the bioactivity or biomolecule of interest, Applicants submit that Thompson fails to disclose the invention process for high throughput screening as defined by Applicants' claim 19. Accordingly, Applicants respectfully submit that Thompson fails to disclose each and every element of claim 19 (and dependent claims 20, 22, 24, 25, 27-29, 35, 37 38 and 43-45) as would be required to establish anticipation under 35 U.S.C. 102(e).

### **The Rejection under 35 U.S.C. § 103**

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

A. Applicants respectfully traverse the rejection of claim 23 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above).

The deficiencies of Thompson described above for disclosing the invention methods of claim 19 apply equally and are incorporated here with regard to claim 23, which depends from claim 19. In addition, Applicants respectfully submit that Thompson fails to suggest the invention methods and would not motivate those of skill in the art to modify Thompson to arrive at the presently presented invention methods because the thrust of Thompson's disclosure is

devoted to preparation and screening of combinatorial gene libraries. Specifically, Thompson's disclosure of "reconstituted metabolic pathways" does not suggest and would not motivate those of skill in the art to look to the DNA of a single donor organism for detection of a "naturally occurring" biomolecule or bioactivity of interest, as the term "naturally occurring" is used in Applicants' specification and claims. Thus, Applicants submit that Thompson's disclosure does not establish *prima facie* obviousness of the invention method of claim 23 under 35 U.S.C. § 103.

**B.** Applicants respectfully traverse the rejection of claims 30-32 and 34 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) and Miao et al, Biotechnology and Bioengineering (1993) 42:708-715, hereinafter "Miao".

Applicants' remarks above regarding the failure of Thompson to render obvious claim 19 and 23 apply equally and are incorporated here. In addition, Applicants submit that the disclosure of Miao fails to remedy the deficiencies of Thompson under 35 U.S.C. § 103 with regard to claim 19, from which claims 30-32 and 34 depend. Miao's disclosure pertains to use of C12FDG as a fluorescent substrate in FACS screening of single bacterial cells of one species (i.e., *E. coli*). Thus, like Thompson, Miao is completely silent regarding screening of a library containing a plurality of clones, wherein each clone contains DNA from a single one of the donor organisms. Indeed, since Miao's disclosure does not pertain to screening of a plurality of species, Applicants submit that the combined disclosures of Thompson and Miao would be insufficient to motivate those of skill in the art to create a method for screening a library of clones containing naturally occurring DNA from a plurality of donor organisms for any purpose, let alone for an activity produced in a clone that triggers fluorescence in a bioactive substrate.

In addition, even if those of skill in the art were motivated by the combined disclosures of Thompson and Miao to arrive at the invention methods, Applicants submit that the cited art would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. Because neither Thompson nor Miao discusses any

technique by which fluorescence screening can be adapted to discover a bioactivity or a biomolecule encoded by DNA from a single donor organism among a plurality of such organisms, those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson and Miao.

Accordingly, Applicants respectfully submit that the combined disclosures of Thompson and Miao, including Miao's disclosure regarding rapid screening using C12FDG, are not sufficient to teach or suggest Applicants' invention of dependent claims 30-32 and 34, which contain the requirements of amended claim 19. Thus, Applicants respectfully submit that claims 30-32 and 34 are not *prima facie* obvious over Thompson, or the combined disclosures of Thompson and Miao.

C. Applicants respectfully traverse the rejection of claim 33 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) and Miao (as above) and further in view of Hirata et al. (U.S. Patent No. 4,861,718; hereinafter "Hirata").

Applicants submit that the remarks above regarding the failure of the combined disclosures of Thompson and Miao to render obvious the invention of claims 19 (and 30-32 and 34) under 35 U.S.C. § 103 apply equally and are incorporated here. The Examiner acknowledges that the combination of Thompson and Miao is not sufficient to block patentability of claim 33 under 35 U.S.C. § 103 (Office Action, page 13, bottom paragraph). In addition, Applicants submit that the disclosure of Hirata fails to remedy the deficiencies of Thompson-Miao disclosure with respect to claim 19. Hirata's disclosure is relied upon by the Examiner as disclosing the heating of a nucleic acid encoding a thermostable beta-galactosidase having a temperature optimum at 70 degrees Celcius. However, like Thompson and Miao, Hirata is completely silent regarding screening of a library containing a plurality of clones, wherein each clone contains DNA from a single one of the donor organisms. Indeed, since Hirata's disclosure does not pertain to high throughput screening of a library of a plurality of

organisms, with each clone containing DNA from only one of the organisms, to determine fluorescence, as is required in amended claim 19, Applicants submit that the combined disclosures of Thompson and Miao and Hirata would be insufficient to motivate those of skill in the art to modify the combined disclosures to arrive at such a method at any temperature.

In addition, even if those of skill in the art were motivated by the combined Thompson-Miao-Hirata disclosures to arrive at the invention methods, Applicants submit that the cited art would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. Because none of the three discusses any technique by which fluorescence screening can be adapted to discover a bioactivity or a biomolecule encoded by DNA from a single donor organism among a plurality of such organisms, those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined Thompson-Miao-Hirata disclosures. Thus, Applicants respectfully submit that claim 33 is not *prima facie* obvious over the cited art.

**D.** Applicants respectfully traverse the rejection of claims 21, 36, 40 and 46 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) in view of Minshull et al. (U.S. Patent No. 5,837,458; hereinafter "Minshull").

The remarks above regarding the failure of Thompson to render obvious under 35 U.S.C. § 103 the invention of claims 19 and 20, from which claims 21, 26 40 and 46 depend, apply equally and are incorporated here. In addition, Applicants submit that the disclosure of Minshull fails to remedy the deficiencies of Thompson acknowledged by the Examiner with regard to the claims at issue (Office Action, page 15, second paragraph). Minshull is relied upon for allegedly disclosing cellular and metabolic engineering by recursive sequence recombination. However, Applicants submit that the combined disclosures of Minshull and Thompson fail to disclose or suggest the invention methods for identifying a bioactivity or biomolecule of interest using high throughput screening of DNA, as defined by amended claim 19, due to failure of either reference to



suggest screening a DNA library containing clones of a plurality of organisms wherein each clone contains DNA of a single one of the organisms to detect those clones containing naturally occurring DNA from one of the organisms that is sufficient to cause the bioactive substrate to fluoresce.

In addition, Applicants submit that even if those of skill in the art were motivated by the combined disclosures of Thompson and Minshull to arrive at the invention methods, the combination of Thompson and Minshull would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. Because neither Thompson nor Minshull discusses any technique by which fluorescence screening can be adapted to discover a bioactivity or a biomolecule encoded by DNA from a single donor organism among a plurality of such organisms, those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised by modification of the combined disclosures of Thompson and Minshull. Accordingly, Applicants submit that prima facie obviousness of claim 33 is not established over the combined disclosures of Thompson and Minshull.

In view of the above amendments and remarks, reconsideration and withdrawal of the various rejections under 35 U.S.C. § 103 are respectfully requested.

In re Application of:  
Short and Keller  
Application No.: 08/876,276  
Filed: June 16, 1997  
Page 15

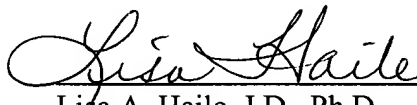
PATENT  
Attorney Docket No.: DIVER1280

**CONCLUSION**

In summary, for the reasons set forth herein, Applicants maintain that the pending claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: 2/6/04



Lisa A. Haile, J.D., Ph.D.  
Reg. No. 38,347  
Telephone: (858) 677-1456  
Facsimile: (858) 677-1465

**USPTO CUSTOMER NUMBER 28213**  
GRAY CARY WARE & FREIDENRICH LLP  
4365 Executive Drive, Suite 1100  
San Diego, California 92121-2133